



NOTES

THROMBOCYTOPENIA

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Acquired/inherited disorders: impaired platelet function, decreased platelet count, sequelae
- Accelerated destruction/consumption → decreased platelets

SIGNS & SYMPTOMS

- Mucocutaneous bleeding (e.g. epistaxis, gingival bleeding, petechiae, purpura)

DIAGNOSIS

LAB RESULTS

- Complete blood count (CBC)
- Peripheral blood smear analysis
- Platelet function tests

TREATMENT

OTHER INTERVENTIONS

- Mitigate complications of deranged platelet function

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

osms.it/heparin-induced-thrombocytopenia

PATHOLOGY & CAUSES

- Acquired platelet disorder
 - Accelerated thrombosis in arteries, veins → consumptive thrombocytopenia.
 - Occurs in individuals exposed to unfractionated heparin/low molecular weight heparin (LMWH)
 - AKA heparin-induced thrombocytopenia thrombosis (HITT)
- Exposure to heparin/LMWH → IgG autoantibodies formed against heparin → platelet factor 4 (PF4) binds to heparin → antibody-heparin-PF4 complex → increased platelet activation → thrombosis formation in arteries, veins

- Increased consumption of platelets for clotting + removal of antibody-heparin-PF4 complexes by macrophages of reticuloendothelial system → thrombocytopenia
 - Thrombocytopenia usually not sufficient to cause significant bleeding
- Classified by severity, timing, degree of drop in platelet count drop, antibody mediation

RISK FACTORS

- 5% individuals exposed to unfractionated/LMWH
 - Unfractionated > LMWH

VISIT...

LANZAROTE
Caliente.COM

- Dose
 - Prophylactic dose > therapeutic doses > intermittent heparin flushes
- More common in individuals who are biologically female

HIT TYPES	
HIT TYPE 1	HIT TYPE 2
Transient, mild, not clinically significant	Complications can be life-threatening
Onset: 1-4 days after exposure	Onset: 5-10 days after exposure
Not antibody mediated; may be caused by heparin-induced platelet aggregation	Antibody mediated (IgG)
Nadir platelet count: 100,000/microL; usually returns to normal, even with continued heparin administration	Mean nadir platelet count: 60,000/microL

COMPLICATIONS

- Venous thromboembolism (VTE)
- Occlusion of large lower limb arteries by platelet rich "white clots" → limb ischemia, necrosis, gangrene, loss of limbs
- Skin necrosis
- Organ infarction
 - Kidney, myocardial infarction; cerebrovascular insult
- Adrenal hemorrhage
 - Adrenal vein thrombosis
- Heparin-induced anaphylactoid reactions

SIGNS & SYMPTOMS

- Skin necrosis at injection site
- Acute systemic reaction after IV heparin bolus
 - Fever with chills, tachycardia, hypertension, dyspnea
- Limb ischemia, organ infarction

DIAGNOSIS

LAB RESULTS

HIT antibody testing

- HIT immunoassay
 - ELISA for anti-PF4 antibodies
 - PF4 antibodies in individual's serum
 - *Colorimetric change*: optical density (OD), HIT antibody concentration
 - Higher OD = higher antibody titer = HIT
- Functional assay
 - Serotonin release assay (SRA)
 - Serotonin release from platelets, ability of HIT antibodies from individual's serum to activate test platelets
 - Release of serotonin + therapeutic heparin concentration
- Heparin-induced platelet aggregation (HIPA) assay
 - Platelet aggregation with no heparin, low/high heparin concentration
 - Minimal platelet aggregation with no heparin, high heparin concentrations; strong aggregation with low heparin concentrations

OTHER DIAGNOSTICS

- History of exposure to unfractionated heparin
- New venous/arterial thrombosis



MNEMONIC: 4Ts

Diagnosis of Thrombocytopenia

Thrombocytopenia: CBC, fall in platelet count

Timing: fall in platelet count, 5–10 days after heparin initiation

Thrombosis: venous/arterial thrombosis, sequelae

Other: no other explanations

TREATMENT

MEDICATIONS

- Immediate discontinuation of heparin
- Administration of non-heparin anticoagulant (e.g. fondaparinux, argatroban)

- Transition to warfarin/other outpatient anticoagulant after stabilization

SURGERY

Thromboembolectomy

- If severe limb ischemia, high risk for amputation

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

osms.it/idiopathic-thrombocytopenic-purpura

PATHOLOGY & CAUSES

- Acquired thrombocytopenia; accelerated immune platelet destruction → bleeding
- AKA, immune thrombocytopenic purpura, autoimmune thrombocytopenic purpura
- B cells produce IgG autoantibodies against platelet glycoproteins (e.g. IIb/IIIa, Ib/IX complexes) → platelets coated with antibodies recognized as “non-self” by splenic macrophages → platelet destruction
 - Contributing factors: impaired platelet production, cell-mediated platelet destruction

malignancy, chronic lymphocytic leukemia

- Alter immune homeostasis
- Alterations in T cell-mediated cytotoxicity/suppression of megakaryocyte production, maturation

Drug-induced immune thrombocytopenia (DITP)

- Triggered by drug-dependent platelet antibodies
- Quinidine, phenytoin, valproic acid, rifampin, trimethoprim-sulfamethoxazole, sulfonamides
- Reaction due to drug/metabolites

Severe ITP

- Platelet counts < 10,000–20,000/microL; significant bleeding requires treatment

Refractory ITP

- Severe ITP, fails to respond to/relapses after splenectomy

TYPES

- Classified by cause, duration, severity

Primary ITP

- Idiopathic

Secondary ITP

- Caused by systemic condition
- Viral infections (most common)
 - HIV, hepatitis C, cytomegalovirus
 - Antibodies against viral antigens cross-react with platelet antigens via molecular mimicry
- Bacterial lipopolysaccharides attach to platelet surfaces → increase phagocytosis of platelets
- Systemic lupus erythematosus, lymphoid

RISK FACTORS

- Age; genetic/acquired factors

COMPLICATIONS

- Potentially severe hemorrhage (uncommon)
 - Intracranial bleeding, subarachnoid hemorrhage, gastrointestinal (GI) hemorrhage, hematuria, severe menorrhagia

SIGNS & SYMPTOMS

- Bruising easily after minor trauma
- Mucocutaneous bleeding
 - Petechiae, purpura, epistaxis, gingival bleeding

DIAGNOSIS

LAB RESULTS

- CBC
 - Low platelet count
- Peripheral blood smear analysis
 - Scarce platelets
- Flow cytometry-based assays
 - Drug-dependent platelet antibodies

OTHER DIAGNOSTICS

- History of drug implicated in DITP



Figure 59.1 Multiple petechiae present in the skin of an individual with ITP. The platelet count was $< 5 \times 10^9/L$.

TREATMENT

MEDICATIONS

Raise platelet count

- High dose glucocorticoids (dexamethasone; prednisone)
- Immune globulin (IVIG)

If no response to above medications

- Rituximab
 - Monoclonal antibody reduces antibody-dependent cytotoxicity, complement-mediated lysis of platelets
- Thrombopoietin (TPO) receptor agonists (e.g. eltrombopag)
 - Increases platelet production by stimulating production of megakaryocytes
- Immunosuppressive agents
 - Danazol, azathioprine, cyclosporine

Medications to avoid

- Antiplatelet agents
 - Aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs)

SURGERY

- If no response to medication

Splenectomy

- Reduces platelet destruction

OTHER INTERVENTIONS

- Platelet transfusions
 - Clinically significant bleeding

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

osms.it/thrombotic-thrombocytopenic

PATHOLOGY & CAUSES

- Thrombotic microangiopathy (TMA) caused by **deficient activity of ADAMTS13 protease**
- ADAMTS13 breaks von Willebrand factor (vWF) molecules** into smaller multimers, prevents excessive accumulation on endothelial surfaces in microvasculature
- Excessive vWF on endothelial surfaces** → increased propensity for platelets to attach, accumulate (esp. in high pressure areas with shearing stress) + endothelial damage → platelet-rich thrombi in microcirculation → tissue ischemia, organ dysfunction, microangiopathic hemolytic anemia (MAHA), thrombocytopenia
- Thrombocytopenia consumptive
 - Increased need for platelets from cyclical clot formation, dissolution
- MAHA
 - Red blood cell (RBC) mechanical fragmentation in microthrombi, damaged vessels → schistocytes
- Organs most affected by TTP in microcirculation
 - Brain, heart, adrenal glands, pancreas, kidneys

CAUSES

- ADAMTS13 deficiency
 - Acquired inhibitory autoantibody (IgG) to ADAMTS13; inherited mutation of ADAMTS13 gene (minority)

RISK FACTORS

- Increased prevalence in individuals who are biologically female, of African

ancestry, diagnosed with systemic lupus erythematosus (SLE)

- Sepsis, liver disease, pancreatitis, cardiac surgery
 - Reduce activity of ADAMTS13
- Pregnancy
 - Decrease in ADAMTS13, increase in vWF, 2nd–3rd trimesters

COMPLICATIONS

- Organ damage
 - Renal insufficiency, focal neurologic/mental status anomalies, arrhythmias

SIGNS & SYMPTOMS

- Classic TTP pentad
 - Thrombocytopenia, MAHA, renal dysfunction, neurologic impairment** (e.g. headache, confusion, seizures, coma), **fever**
- Mucocutaneous bleeding
 - Petechiae, purpura (coalesced petechiae), epistaxis, gingival bleeding
- Intravascular hemolysis → dark urine
- Lightheadedness, abdominal pain, easy bruising, nausea/vomiting



MNEMONIC: RAFT'N

Common signs of Thrombotic thrombocytopenia purpura

Renal problems

Anemia: MAHA associated

Fever

Thrombocytopenia

Neurologic dysfunction

DIAGNOSIS

LAB RESULTS

- CBC
 - Decreased platelet count
 - Increased reticulocyte count
 - Decreased hemoglobin, hematocrit
- Peripheral blood smear analysis
 - Schistocytes, spherocytes
- Hemolysis
 - Elevated lactate dehydrogenase (LDH)
 - Elevated indirect bilirubin
 - Reduced haptoglobin
- Elevated creatinine
 - Renal insufficiency

OTHER DIAGNOSTICS

- ADAMTS13 assay
 - Gel electrophoresis of VWF multimers measures degradation by ADAMTS13
- ADAMTS13 inhibitor assay
 - Autoantibody titer
- Genetic testing
 - ADAMTS13 gene mutation, if hereditary TTP suspected

TREATMENT

MEDICATIONS

- Glucocorticoids
- Monoclonal antibody

OTHER INTERVENTIONS

- Plasma exchange (PEX)

LAB VALUES IN THROMBOCYTOPENIC DISORDERS

	TTP	ITP	HIT
PLATELETS	↓↓↓	↓↓↓	↓↓
HEMOGLOBIN	↓↓	Normal	Normal
LDH	↑↑↑	Normal	Normal
INDIRECT BILIRUBIN	↑	Normal	Normal
HAPTOGLOBIN	↓	Normal	Normal
RETICULOCYTES	↑	Normal	Normal
SCHISTOCYTES	↑↑↑	Normal	↑